Commentary on *The Maximization Test*

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Origins John Draize of the FDA published a procedure for identifying contact allergens, using human volunteers. It became known as the ''repeated insult test'' and was supposed to be an improvement on the Schwartz-Peck test, also under FDA sponsorship. Though Draize's method did not have the force of law, it came to be regarded as a quasi-legal regulation which put a manufacturer of a topical drug at risk if the repeated insult test had not been done.

To Dr. Kligman's astonishment, he could not find any published data which validated Draize's test. He questioned the number of subjects and exposures. Why 200 subjects? Perhaps 100 would suffice? Why ten exposures, instead of 5, or 15 or 100? Subsequently, he learned there was a file in the FDA archives, which on the basis of unpublished experience with many topical agents, justified Draize's specifications.

Dr. Kligman reasoned that the Draize test was ''based not on experimentation but on revelations originating in outer space.'' Clinical experience had demonstrated that creams containing penicillin were strongly allergenic, forcing them off the market. Also, topical neomycin was known to have an appreciable risk of sensitization. Certain topical bleaching agents, notably monobenzyl ether of hydroquinone, which were effective only when applied daily for many months, could not continue to be used because a substantial percentage of patients became sensitized.

The stage was set for the important, and impertinent, question. Would these well-known allergens be detected by the Draize repeated insult test on 200 subjects? Dr. Kligman had available a large population of prisoner volunteers on whom the Draize test could be tested for its validity.

The result was stunningly negative. This ''exalted, exaggerated, formidable procedure was incapable of recognizing sensitizers.'' It almost guaranteed that a formulation would pass with flying colors. In a ''kinky'' sort of way, this lack of sensitivity may actually have increased the reputation and commercial usefulness of the test. After all, positive results hang a cloud of allergenicity over a product which might be otherwise quite useful. Benzoyl peroxide is an example of a useful drug which is potentially a strong allergen. On the other hand, failure to detect allergenic substances that are used daily can have disastrous effects. For instance, the manufacturers of tetrachlorosalicylanilide claim to have done three separate 200-subject Draize tests in different facilities without discovering that this bacteriostat, incorporated in soaps, was a potent allergen. Had that been known, the calamitous epidemic of photoallergy could have been averted.

Development of the Maximization Test Dr. Kligman set out to establish a simplified procedure which could consistently identify contact sensitizers and which could also rate these according to their sensitization potential, from weak to strong. Dermatologists knew that sensitization was far more likely when agents were applied to dermatitic, damaged skin. He took advantage of sodium lauryl sulfate to induce a localized irritant dermatitis. Being an anionic surfactant it had the further virtue of making the horny layer barrier extremely permeable.

The upshot was that with 25 subjects, exposed to 5–48 h patch tests, known allergens could be identified and ranked by potency. The exposure conditions were chosen to use every means to facilitate sensitization, so as to avoid false negative results, hence the name, *The Maximization Test.*

World wide experience has demonstrated the specificity and sensitivity of the test.

Comment It would be difficult to develop The Human Maximization test in today's political and legal climate. Consequent to the publication of the test, Dr. Kligman was vilified for his use of prisoner volunteers for his studies. As a colleague of Dr. Kligman's for 6 years, nothing is more absurd to me than the accusation that he is a ''racist'' or ''fascist.'' Dr. Kligman throughout his career has demonstrated humanity and generosity; his intellectual and financial support of medical education and medical research has been exemplary.

The development of the maximization test should be considered in historical context. Over the past 20 years, there have been growing controls upon biomedical investigation. The development of active institutional review committees for human clinical research and animal rights committees for animal related research is now a reality. Unquestionably, these review procedures have heightened awareness of responsible behavior by experimentalists involved in animal and human research. However, there are times when one questions whether the regulations serve the needs of patients, experimental animals, or the bureaucracies themselves. There are recent major initiatives to find alternatives to animal testing. This is a welcome step, but the interdiction of responsible *in vivo* evaluation of topical agents can be a serious blow to progress in cutaneous biology.

Albert Kligman's Maximization test is a landmark in cutaneous pharmacology. It has provided a unique method to evaluate topical agents. It is also a very important reference point in the complex, philosophic and sociologic evolution of bio-medical investigation. One hopes that contributions such as Dr. Kligman's will be possible in the future [1,2].

REFERENCES

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